Applicants submit that the claims recite a "method of screening for **autoimmune disease associated with a reduction in NFκB activity**". Thus the claims to not encompass *any* autoimmune disease as asserted by the Examiner, but in fact relate to those autoimmune diseases which are associated with reduced NFκB activity.

The specification identifies a variety of autoimmune diseases whose effects may be correlated with reduced proteolytic processing of NFκB, including Addison's disease (page 29), ulcerative colitis and Crohn's disease (page 31), lupus erythematosus (page 31), Sjörgen's syndrome (page 32), Type I diabetes (page 33-34), multiple sclerosis (page 35), rheumatoid arthritis (page 36), Hashimoto's disease (page 37), Grave's disease, vitiligo (page 37), psoriasis (pages 37-38), pemphigus vulgaris (page 38), and others. Despite the different clinical manifestations of these diseases, they share many physiological responses in common, such as fatigue, inflammation, paresis, joint stiffness, pain or swelling, skin lesions or nodules, skin discoloration, enzymatic imbalances, and tissue degeneration, which may be used as common diagnostic indicators of the presence of an autoimmune disease (see page 8 of the specification, last paragraph through page 9, bridging paragraph; see, also U.S. Patent No. 5,962,516, column 2, lines 26-28; U.S. Patent No. 5,888,511, column 2, lines 10-13; and U.S. Patent No. 5,506,213, column 3, line 65, through column 5, line 60; provided in Applicants' Supplemental Information Disclosure Statement (SIDS) filed April 12, 2001). Indeed, the prior art supports a finding of common genetic susceptibility loci involved in the pathogenesis of autoimmune diseases. See, e.g., as discussed in Becker et al., Proc. Natl. Acad. Sci. USA 95(17): 9979-9984, 1998 and Heward et al., Clinical Science 93: 479-491, 1997, provided with Applicants' SIDS further supports the use of assays to identify defects in the products of "master genes" or common loci shared in multiple autoimmune diseases. As discussed in Becker et al, *supra,* at page *7 (of the web-published article), last paragraph, "shared genes among distinct [autoimmune] diseases may lead to common early diagnostic criteria and therapeutic strategies."

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Applicants submit that a central premise of the invention is that many autoimmune diseases share a common etiology. There are many indicators in the art that point to autoimmune diseases being related (see below), and the current invention demonstrates unequivocally that autoimmune diseases are mechanistically linked by a deficiency in NFκB activation. Hence, Applicants submit that restoring NFκB activity can treat autoimmune diseases. Applicants submit the following pertinent observations in support of this conclusion.

Applicants submit that genetic studies on a number of autoimmune diseases including Insulin Dependent Diabetes (IDDM), rheumatoid arthritis, multiple sclerosis and SLE have shown that approximately 15 to 30% of pairs of monozygotic twins show disease concordance compared with 5% of dizygotic twins (Harrison's Principles of Internal Medicine, 15th Edition McGraw-Hill Medical Publishing Division; www.harrisonsonline.com; Part 12, section 1, chapter 307, page 2; Exhibit A). Clustering of different autoimmune diseases in a same family is frequently observed and indicates a common genesis between different autoimmune diseases (see Familial autoimmunity and the idiopathic inflammatory myopathies by Shamim EA, Miller FW. Curr Rheumatol Rep 2000 2(3):201-11; Exhibit B). For example, Sjögren's Syndrome (SS) often occurs in conjunction with rheumatic diseases, such as lupus and rheumatoid arthritis, of known or suspected autoimmune origins. Applicants therefore contend from the above citations that autoimmune diseases share a common genesis and that there is genetic evidence in the art which supports this assertion.

Applicants submit that genetic studies published both prior to and subsequent to the filing date of the present invention also indicate that the transcription factor NFκB is a central, indeed pivotal, component in the etiology of many autoimmune diseases as disclosed in the present invention. For example, Hugot et al have demonstrated that susceptibility to Crohn's disease, a chronic inflammatory autoimmune disorder of the gastrointestinal tract, requires NOD2, a protein that activates NFκB (Hugot et al.(2001) Nature 411, 599 – 603; Exhibit C; Ogura et al. (2001)

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Nature 411, 603 - 606 (2001); Exhibit D). Genetic studies by Hegazy et al also implicate NFκB in the etiology of insulin dependent diabetes (Hegazy et al. Genes Immun 2001 Oct;2(6):304-8). In addition, it is well known in the art that deficiency in NFκB/rel A, abolishes both T and B cells' immunogenic responses to an antigen (reviewed Gerondakis et al. (1999) Oncogene 18, 6888-6895; Exhibit E) and that immunogenic and autoimmune antigens elicit a series of lymphocyte-specific signaling events that ultimately converge on and activate the transcription factor, NFκB (reviewed in Goodnow, C., 2001 Lancet 357, 2115-2121; Exhibit F). Current therapeutics such as glucocorticoids, chloroquine and gold compounds that are used to treat autoimmune diseases, target the NFκB signaling pathway (see Barnes, P. J. Clin. Sci. (1998) 94, 557-72; Exhibit G). One of skill in the art would therefore find no reason to not conclude from the genetic evidence, *supra*, that numerous autoimmune diseases according to the invention are mechanistically linked and that this common mechanism involves the transcription factor NFκB. Clearly, the state of the art at the time the present application was filed, and the substantial scientific data published subsequent to Applicants filing date supports Applicants premise that autoimmune diseases are related and that this relationship revolves centrally around aberrant NFkB activity.

It is well known that NFκB plays a central role in regulating physiological responses to autoimmune disease by regulating the expression of cytokines, cell adhesion molecules, and other proteins (see, as discussed in Adams, WO 96/13266, Kopp and Ghosh, Science 265: 956-969, 1994, and Grilli, et al., Science 274: 1384-1385, 1996, cited in the specification at page 7, and Grilli, et al., Int. J. Cytology 143: 1-62, 1993, cited at page 43; each of these references having been provided with Applicants' Information Disclosure Statement (IDS), filed October 6, 1998; see, also U.S. Patent No. 6,117,911, Example VII, provided with Applicants' response of April 12, 2001). Thus, the use of NFκB to identify malfunctions in the common processes implicated in the pathogenesis of autoimmune responses is well supported by both Applicants' specification and the prior art.

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The Examiner has acknowledged that the specification is enabling for a method of screening for diabetes by detecting a reduction in the proteolytic processing of NFκB, apparently, because Applicants have exemplified the success of their method using NOD mice (e.g., Example 2). However, NOD mice are not solely animal models for the specific symptoms presented in Type I diabetes mellitus. The NOD mouse spontaneously gets type I diabetes, rheumatoid arthritis, Sjogren's syndrome, autoimmune hemolytic anemia, and auto antibodies reminscent of a lupus-like diesase (Research in Immunology 148: 301-306, 1997; Exhibit H; and discussed in the specification at page 39, lines 3-4). Thus the NOD mouse is an art recognized animal model for at least five specific autoimmune diseases. Further, as discussed in the specification at page 40, lines 24 through bridging paragraph on page 41, NOD mice can be considered as models of some of the common processes observed in *all* autoimmune diseases by virtue of the abnormal antigen presentation and processing observed in these mice. Therefore, Applicants' finding that NOD mice lack the proteosome-processed, active form of NFκB (see page 88, lines 16-18, of Applicants' specification), in view of all that is known in the prior art about the relationship between NFκB activity and universal autoimmune disease processes, such as inflammation and tissue destruction (see, as discussed in the references cited in the previous paragraph), provides an ample expectation of success for an assay for screening for the presence of an "*autoimmune disease associated with a reduction in NFκB activity*" as claimed in the present application.

To enable the present invention as claimed, the specification must teach one of ordinary skill in the art how to make and use the present invention as claimed. To meet this requirement, the specification must teach how to obtain a biological sample from a mammal; assays for measuring the level of proteolytic products derived from NFκB processing; and the correlation of such measurements with a sufficient number of autoimmune diseases to enable the genus of autoimmune diseases associated with a reduction in NFκB activity. Applicants submit that the specification, accordingly, teaches the following.

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1. Page 9, lines 15-22 define a "biological sample". Such a sample includes whole organisms, or subsets of its tissues, cells or parts, including fluids, homogenates, lysates, or extracts. A biological sample also includes nutrient medium which contains cellular components. Applicants submit that one of skill in the art would be able to readily obtain a biological sample based on the state of the art at the time the present application was filed. It is well established that Applicants are not required to re-teach that which is already routine in the art (see, for example, *In re Skrivan,* 166 U.S.P.Q. 85, 88 (C.C.P.A. 1970)).

2. Page 23, line 21 though page 25, line 20, and page 67 teaches methods for detecting defects in proteolytic activity and proteolytic processing.

3. Page 79-92 (Examples 1 and 2) teach that the NOD mouse, an animal model which is well established as a model for several autoimmune diseases, is defective for NFκB activity and signalling. In particular, page 88, lines 19-20 and 24 teach that the NFκB defect appears to be a defect in NFκB activation, that is, defective proteasome processing of NFκB. Thus, the specification teaches a correlation between at least five autoimmune diseases which are associated with a reduction in NFκB activity, and impaired proteasome processing of NFκB.

In view of the above arguments, Applicants respectfully submit that the specification is fully enabling for the claimed invention, that is, a method of screening for autoimmune diseases *associated with a reduction in NFκB activity.*

The Examiner asserts that the state of the art "does not recognize the use of detecting a reduction in the proteolytic processing of NFκB by proteosomes for detecting...autoimmune diseases". Applicants concur. However, Applicants respectfully submit that the Examiner's statement is not a valid reason on which to base an enablement rejection, but is, in fact, a summary of what makes an invention inventive. Applicants submit that it is this very divergence from what is recognized in the art which makes the present invention novel and unobvious.

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Applicants respectfully submit that the if the predictability of an invention for purposes of meeting the enablement requirement was predicated upon the invention modeling itself after the prior art, then no patent would ever issue, as no invention would be novel.

The Examiner also asserts that autoimmune disease penatrance in the NOD mouse is not always complete, and that not all genetically NOD mice develop autoimmune disease. Applicants submit that this is not fatal to a finding of enablement. The NOD mouse is an art-recognized animal model of at least five autoimmune diseases. A search of the MEDLINE database using the terms "NOD and autoimmune" retrieved 1172 references, published over a period of 19 years. Applicants thus submit that the state of the art recognizes the NOD mouse as a tested, reliable, and accurate model in which to study autoimmune disease. The present specification has demonstrated, by working examples, that NFκB processing and activation is impaired in an animal model of at least five different autoimmune diseases, and that decreased proteolytic processing of NFκB is thus predictive of autoimmune diseases "associated with a reduction in NFκB activity".

Accordingly, Applicants respectfully submit that the specification is fully enabling for the claimed invention. Applicants respectfully submit further that the rejection is thus improper and should be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

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Respectfully submitted,

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Marked-up Version of Claim Amendment

65. (Twice amended) A method of screening for autoimmune disease associated with a reduction in NFkB activity in a mammal deemed to be at risk for an autoimmune disease comprising:

a) providing a biological sample from a mammal; and

b) [detecting activity of proteasomes in said sample by] measuring the level of proteolytic products derived from the proteolytic processing of NFκβ [by said proteasomes generated by said proteasomes] <u>in said sample</u>, wherein a reduction in the level of said proteolytic products from a basal state is correlated with the presence of an autoimmune disease associated with a reduction in NFκβ activity.